original article

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Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG)

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For the International Breast Cancer Study Group

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Background: We sought to determine whether a high-risk group could be defined among patients with operable breast cancer in whom a search of occult central nervous system (CNS) metastases was justified.

Patients and methods: We evaluated data from 9524 women with early breast cancer (42% node-negative) who were randomized in International Breast Cancer Study Group clinical trials between 1978 and 1999, and treated without anthracyclines, taxanes, or trastuzumab. We identified patients whose site of first event was CNS and those who had a CNS event at any time.

Results: Median follow-up was 13 years. The 10-year incidence (10-yr) of CNS relapse was 5.2% (1.3% as first recurrence). Factors predictive of CNS as first recurrence included: node-positive disease (10-yr = 2.2% for > 3 N+), estrogen receptor-negative (2.3%), tumor size > 2 cm (1.7%), tumor grade 3 (2.0%), < 35 years old (2.2%), HER2-positive (2.7%), and estrogen receptor-negative and node-positive (2.6%). The risk of subsequent CNS recurrence was elevated in patients experiencing lung metastases (10-yr = 16.4%).

Conclusion: Based on this large cohort we were able to define risk factors for CNS metastases, but could not define a group at sufficient risk to justify routine screening for occult CNS metastases.

Key words: breast cancer, central nervous system, adjuvant chemotherapy, competing risks, CMF, metastases

introduction

In women with breast cancer, a population-based estimate of the incidence proportion of brain metastases is 5.1% [1]. Based on case series, the incidence of clinically evident central nervous system (CNS) metastases among women with metastatic breast cancer is estimated to be 10% to 16% [2, 3]. In autopsy series, brain metastases are found in 20% to 30% of patients. To our knowledge, the present report is the first series on a large cohort of patients with long-term follow-up (median 13 years) from the diagnosis of early-stage breast cancer which analyzes factors associated with CNS recurrence. The purpose of this report is to determine whether there is a patient population with a risk of CNS metastases high enough to justify routine screening for CNS recurrence.

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patients and methods

We analyzed data from 9524 patients with early breast cancer who were entered onto International Breast Cancer Study Group (IBCSG; formerly the Ludwig Breast Cancer Study Group) trials I through IX [4–10] between 1978 and 1999 (Table 1). Clinical, hematological and biochemical assessments of each patient were required every three months for two years, every six months until the end of the fifth year and yearly thereafter until death. All sites of disease relapse, including the first and subsequent events until death, were recorded in the study databases. In trials I-V, chest X-rays and bone scans were required every six months for two years and once yearly up to five years. These tests were recommended beyond the fifth year only if clinically indicated. In trials VI, VII and VIII, chest x-rays and bone scans were required but further tests were performed only

Table 1. Characteristics of IBCSG Trials I through IX

Trial	Population	Years of accrual	No. of eligible patients	Treatment groups	Median follow-up (years)
I	Premenopausal women with 1–3 Pos nodes	1978–1981	491	CMF×12 CMFp×12	23
II	Premenopausal women with ≥ 4 Pos nodes	1978–1981	327	CMFp×12 Ox + CMFp×12	22
III	Postmenopausal women < 65 years old	1978–1981	463	Observation p + T×12 CMFp + T×12	23
IV	Postmenopausal women 66–80 years old	1978–1981	320	Observation p + T×12	22
V	Pre- or postmenopausal women with Neg nodes	1981–1985	1275	Observation PeCMF	19
V	Pre- or postmenopausal women with Pos nodes	1981–1985	1229	PeCMF CMFpT×6 PeCMF + CMFpT×6	18
VI	Premenopausal women with Pos nodes	1986–1993	1475	CMF×6 CMF×6 + reint CMF×3 CMF×3 + reint	13
VII	Postmenopausal women with Pos nodes	1986–1993	1212	T T + delayed CMF T + CMF×3 T + CMF×3 delayed CMF	13
VIII	Premenopausal women with Neg nodes	1990–1999	1063	Goserelin×24 mos. CMF×6 CMF×6 → Gos×18 mos.	8
IX	Postmenopausal women with Neg nodes	1988–1999	1669	T×5 years CMF×3 → T×57 mos.	9

Abbreviations: Pos, positive; Neg, negative; C, cyclophosphamide 100 mg/m^2 orally (PO) days 1–14 of each cycle; M, methotrexate 40 mg/m^2 intravenously (IV) days 1 and 8 of each cycle; F, fluorouracil 600 mg/m^2 IV days 1 and 8 of each cycle; p, prednisone 7.5 mg/d PO; Ox, oophorectomy; T, tamoxifen 20 mg PO once daily; PeCMF, perioperative CMF; reint, reintroduction of 3 cycles of CMF; delayed CMF, 3 cycles of CMF 9, 12, and 15 months after randomization; goserelin, monthly subcutaneous implants at 3.6 mg.

following clinical indications. In trial IX further tests were recommended only if clinically indicated.

For all trials, ER concentrations of greater than or equal to 10 fmol/mg of cytosol protein by ligand-binding assay were considered positive; lower values were considered negative. Steroid hormone receptor determination by immunohistochemistry was allowed later in trials VI through IX. The cohort of patients with node-positive, ER-negative disease was prospectively defined as high risk population of interest.

Centrally assessed HER2 was available for a subgroup of 3871 patients from trials V, VIII, and IX, and was evaluated using immunohistochemistry. Central immunohistochemical analysis for patients in trial V (n = 1506) was performed in 1991 using the monoclonal antibody ICR12, which recognizes the external domain of the c-*erb*B-2 protein. The antibody was titrated to only stain tumors that showed amplification [11] and would thus be equivalent to 3+ using current criteria. For trials VIII–IX (n = 2365) HER2 was evaluated in 2002 according to the 4 tiers (from 0 to 3+) FDA-approved scoring system, taking into account the percentage of immunoreactive cells in the invasive component of the tumors, and the intensity and completeness of membrane staining [12]. For trials VIII-IX 3+ is considered HER2-positive. The subset of patients that have HER2 status available is largely node-negative (81%).

All patient data, including data regarding disease- and survival-related events, were reviewed and classified by the medical study coordinators (A.G. and M.C.-G.).

statistical methods

Cumulative incidence functions were used to estimate the percentage of patients who experienced the various competing events within the study cohorts rather than the overestimated percentages obtained with the Kaplan-Meier method based on the cause-specific hazards [13–15]. Differences between the cumulative incidence functions according to patient subgroups were tested for statistical significance using the procedure of Gray [16]. Analyses were conducted to determine whether the risk of recurrence in CNS increased according to baseline characteristics or after a first recurrence elsewhere. A cumulative incidence function regression model of Fine and Gray [17] was used for multiple regression analyses. Covariates included in the model were nodal status, pathologic tumor size, tumor grade, estrogen receptor status, menopausal status, and age. Overall survival from the time of CNS recurrence was estimated using the method of Kaplan and Meier [18]. P values are two-sided.

categories of sites of recurrence

First breast cancer recurrence events were classified according to their sites. Local recurrences were confined to the ipsilateral conserved breast or ipsilateral chest wall (with or without mastectomy scar involvement). Regional recurrences involved ipsilateral axillary, supraclavicular, and/or internal mammary lymph node metastases. Distant recurrences involved soft tissue, bone, and visceral metastases, including CNS and all other organ involvement and diffuse intra-abdominal metastases. Other first

events, including contralateral breast cancer, non-breast cancer second malignancies, and death without malignancy, were also recorded. Time to first event was defined as time from randomization to the occurrence of a first event of any type. An event was considered to be a component of a first event if diagnosed within a 2-month time frame.

Occurrence of CNS metastases as the first site of recurrence with or without recurrence at any other site was the event of interest. Diagnosis of CNS recurrence was based on clinical assessment. At the time of relapse CNS imaging was not performed unless there was a clinical suspicion of CNS recurrence. All other sites of first recurrence (not CNS) and any other event, such as, contralateral breast cancer, non-breast cancer second primary tumors, and death without recurrence, were considered competing events. The sum of the cumulative incidence of CNS metastases plus the cumulative incidence of the other competing events equals the cumulative incidence of a first event of any type. In this retrospective analysis it was not possible to distinguish between parenchymal brain metastases and leptomeningeal disease. Since leptomeningeal disease is reportedly five times less frequent than parenchymal brain metastases [2], this study essentially discusses the latter.

In addition to site of first recurrence, we calculated cumulative incidence of CNS events at any time (either as first event or as subsequent recurrences). Time to CNS recurrence at any time was defined as the time from randomization to the time of CNS recurrence whether it was a first or subsequent event. Death before CNS recurrence was considered the only competing event in this analysis. Patients experiencing neither CNS recurrence nor death were censored at the time last known to be alive without CNS recurrence.

We analyzed the cumulative incidence of subsequent CNS metastases according to sites of first recurrence. The time to subsequent recurrence was measured from the time of the first recurrence; death without subsequent CNS recurrence was the only competing event. CNS recurrence was observed at autopsy for 28 patients (0.3%). For this report, these 28 cases were included in the analysis as competing risks for estimating the incidence of CNS recurrence.

results

Included in the analysis were 9524 eligible patients from IBCSG trials I through IX (Table 1), and patient characteristics are shown in Table 2. The sites of first event are shown in Table 3. At a median follow-up of 13 years, 46.2% of all patients were alive without recurrence; 53.8% (5122 of 9524) experienced a first event, namely disease recurrence at known sites ($n = 3937$), contralateral breast cancer ($n = 384$), failure at an unknown site ($n = 36$), a non-breast cancer second primary ($n = 389$), or death without recurrence ($n = 376$). Overall, CNS was a component of first recurrence in 1.3% of patients (126 of 9524). Fifty-five patients (0.6%) experienced a CNS recurrence concurrently (within 2 months) with other sites as a first event.

The site-specific cumulative incidences of CNS metastases and other competing events as first recurrence are shown in Figure 1. At 10 years from study entry, the cumulative incidence of CNS metastases as components of first recurrences was 1.3%, and the cumulative incidence of competing first events was 47.2%. At 10 years, the total cumulative incidence of recurrence due to any cause as a first event was 48.5% (1.3% + 47.2%).

Table 4 lists the cumulative incidences of CNS metastases as site of first recurrence and competing events at 2, 5, 10 and 15 years from randomization, for the overall population and for subpopulations defined according to lymph node involvement, tumor grade, pathologic tumor size, ER status, the combination of ER and lymph node status (ER-negative with positive nodes versus other), HER2 status, menopausal

Table 2. Patient and tumor characteristics

	No. of patients	Percentage
Total cases	9524	100.0
Mastectomy	7371	77.4
Breast-conserving surgery with radiotherapy	2153	22.6
0 positive nodes	4007	42.1
1–3 positive nodes	3354	35.2
4 or more positive nodes	2163	22.7
Tumor grade 1	1451	15.2
Tumor grade 2	4142	43.5
Tumor grade 3	3352	35.2
Tumor grade unknown	579	6.1
Tumor size ≤2cm	4545	47.7
Tumor size >2cm	4678	49.1
Tumor size unknown	301	3.2
ER-positive	5457	57.3
ER-negative	2481	26.0
ER-unknown	1586	16.7
ER-negative and positive nodes	1473	15.5
Other*	6465	67.9
ER-unknown	1586	16.6
HER2-negative	3263	34.3
HER2-positive	608	6.4
HER2 unknown	5653	59.4
Premenopausal	4763	50.0
Postmenopausal	4761	50.0
Age < 35 years	372	3.9
Age 35–49 years	3542	37.2
Age 50–59 years	2936	30.8
Age ≥ 60 years	2674	28.1

*Subgroup defined as not node-positive with ER-negative primary tumors.

Table 3. Sites of first event

	No. of patients	Percentage
Total patients	9524	100.0
Events	5122	53.8
Deaths	4043	42.5
Sites		
Local	796	8.4
Contralateral breast	384	4.0
Regional	549	5.8
Distant: soft tissue, nodes	158	1.7
Distant: bone	1052	11.0
Distant: viscera*	1382	14.5
Second (non-breast) primary	389	4.1
Death w/o recurrence	376	3.9
Unknown	36	0.4

*126 of the 1382 were CNS recurrences; 1.3% of the population.

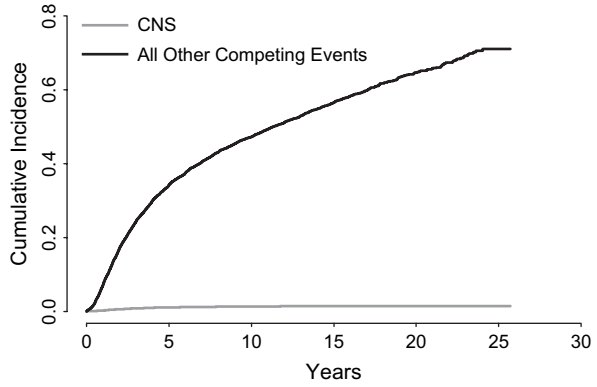

Figure 1. Cumulative incidence of CNS metastases and other competing events as first recurrences among 9524 patients. Time was measured from the date of randomization.

status, and age. Significant differences across categories of lymph node status, tumor grade, pathologic tumor size, ER status, HER2 status, and the combination of ER and lymph node status were observed in univariate analyses among patients with recurrence in CNS. Patients with node-positive disease and ER-negative primary tumors at the time of diagnosis were prospectively defined as a group of interest expected to show a higher risk of CNS recurrence. This subgroup had 2- and 10-year cumulative incidence of CNS as first event of 1.5% and 2.6%, respectively ($P < 0.01$). Among patients presenting with four or more involved nodes, the cumulative incidence of CNS metastases as first event was 1.3% at 2 years and 2.2% at 10 years ($P < 0.01$). The incidence of CNS disease was significantly higher among patients with ER-negative primary tumors, with a 10-year cumulative incidence of 2.3% noted, compared with an incidence of 0.9% among patients with ER-positive primary tumors ($P < 0.01$), and patients with HER2-positive tumors with a 10-year cumulative incidence of 2.7% compared with 1.0 for those with HER2-negative tumors ($P < 0.01$). Larger tumor size was predictive of a significantly higher incidence of CNS involvement at 10 years (1.7% versus 0.9%; $P < 0.01$). Also, the incidence of CNS disease was significantly higher among patients with grade 3 tumors, with a 10-year cumulative incidence of 2.0%. All significant factors retained statistical significance in the multiple regression analyses (results not shown).

The cumulative incidences of recurrence in CNS at any time (whether first or subsequent recurrence) are listed in Table 5. CNS was a site of recurrence at any time in 5.4% of patients. Fifty-seven percent of patients were still alive without CNS metastases, and 37.1% had died without known CNS metastases. The 10-year cumulative incidence of CNS recurrence at any time was 5.2% (Figure 2A). Among patients presenting with four or more involved nodes, the cumulative incidence of CNS metastases at any time was 2.3% at 2 years from randomization and 8.5% at 10 years (Figure 2B). The cumulative incidence of CNS metastases at any time was significantly higher among patients with ER-negative tumors than among patients with ER-positive tumors (7.8% versus 4.0% at 10 years; $P < 0.01$) We note with interest the different patterns of the risk of death across time for cohorts defined by ER status. (Figure 2C). Among patients with grade 3 tumors, the cumulative incidence of CNS metastases at any time was 1.9% at 2 years from randomization and 7.8% at 10 years (Figure 2D). In patients with HER2-positive disease, the 10-year cumulative incidence of CNS disease was higher than among patients with HER2-negative disease (6.8% versus 3.5% at 10 years; $P < 0.01$; Figure 2E). In the high risk cohort of patients with node-positive disease and ER-negative primary tumors, the cumulative incidence of CNS metastases at any time was significantly higher than among patients in the cohort without node-positive disease and ER-negative primary tumors (8.7% versus 4.4% at 10 years; $P < 0.01$; Figure 2F). Younger patients (< 35 years), those with larger tumors, and premenopausal patients also had significantly higher incidences of metastases in CNS (all $P < 0.01$). Again, these factors remained statistically significant in the multiple regression analyses (results not shown).

A total of 391 patients experienced a subsequent CNS recurrence after a first recurrence elsewhere (Table 6). Site of first recurrence was recorded as viscera for 135 (34.5%) and bone for 85 (21.7%) of these 391 patients. When viscera was the first site of recurrence ($n = 1256$; excluding the 126 CNS events classified as viscera as site of first recurrence), a subsequent CNS recurrence occurred in 10.7% (135 of 1256) of cases. The cumulative incidence of a subsequent recurrence in CNS among the 1256 patients whose first recurrence was viscera was 7.6% at 2 years and 11.4% at 10 years after the first recurrence. When bone was the first site of recurrence, a subsequent CNS recurrence occurred in 8.1% (85 of 1052) of cases. The 2- and 10-year cumulative incidence of a subsequent recurrence in CNS among the 1052 patients whose first recurrence was bone was 4.6% and 8.6%, respectively.

Within the cohort of 577 patients who experienced lung metastasis as site of first recurrence (excluding 26 patients who had concurrent sites in the CNS and lung), 90 (15.6%) patients experienced a subsequent recurrence in CNS. The cumulative incidence of a subsequent recurrence in CNS among the 577 patients whose first recurrence was lung was 10.6% at 2 years and 16.4% at 10 years after the first recurrence (Table 6).

We also examined the relationship between the number of documented metastatic sites and CNS recurrence. The proportion of CNS recurrences increased as the number of metastatic sites increased (data not shown).

Five hundred and seventeen patients experienced a CNS recurrence at any time (whether first or subsequent recurrences). The median survival after CNS recurrence was 4 months, and only 20% of these patients survived beyond 1 year (Figure 3). In view of the dismal overall prognosis, it is surprising that four patients have survived 4.5 years beyond CNS recurrence. Therapeutic information was available for three of these four cases. In all three cases, CNS recurrence was treated with surgical excision, while radiotherapy was added for two of the three cases.

discussion

Despite treatment, the prognosis after CNS recurrence in breast cancer is dismal [2, 3], with a survival rate of only 20%

Table 4. Site-specific cumulative incidence: site of first recurrence (measured from date of randomization)

	No. of patients	No. of events	% of patients	Incidence (%)				
				2-year	5-year	10-year	15-year	*P*
Site of first recurrence: CNS								
Total	9524	126	1.3	0.5	1.1	1.3	1.4	
Nodal status								
Node-negative	4007	32	0.8	0.2	0.6	0.8	0.8	<0.01
1–3 positive nodes	3335	45	1.3	0.4	1.1	1.3	1.4	
≥4 positive nodes	2163	49	2.3	1.3	1.9	2.2	2.3	
Tumor grade								
1	1451	8	0.6	0.1	0.4	0.5	0.7	<0.01
2	4142	40	1.0	0.3	0.8	1.0	1.0	
3	3352	65	1.9	0.9	1.7	2.0	2.0	
Pathologic tumor size								
≤2 cm	4545	41	0.9	0.3	0.7	0.9	1.0	<0.01
>2 cm	4678	80	1.7	0.7	1.4	1.7	1.8	
ER status								
ER-negative	2481	57	2.3	1.1	1.9	2.3	2.4	<0.01
ER-positive	5457	49	0.9	0.3	0.7	0.9	0.9	
ER status and nodal status								
ER-negative and positive nodes	1473	39	2.6	1.5	2.3	2.6	2.7	<0.01
Other	6465	67	1.0	0.3	0.8	1.0	1.1	
HER2 Status								
HER2-negative	3263	30	0.9	0.2	0.7	1.0	1.0	<0.01
HER2-positive	608	16	2.6	1.2	2.3	2.7	2.7	
Menopausal status								
Pre menopausal	4763	71	1.5	0.5	1.2	1.5	1.5	0.17
Post menopausal	4761	55	1.2	0.6	0.9	1.1	1.2	
Age								
<35 years	372	8	2.2	0.8	1.9	2.2	2.2	0.21
35–49 years	3542	47	1.3	0.5	1.0	1.3	1.4	
50–59 years	2936	44	1.5	0.7	1.3	1.5	1.5	
≥60 years	2674	27	1.0	0.4	0.7	1.0	1.1	
Competing risks†								
Total	9524	5009	52.6	17.2	34.2	47.2	56.5	
Nodal status								
Node-negative	4007	1325	33.1	8.8	19.6	30.8	40.1	<0.01
1–3 positive nodes	3335	1962	58.5	15.6	35.0	48.6	58.1	
≥ 4 positive nodes	2163	1722	79.6	35.2	59.7	73.5	80.0	
Tumor grade								
1	1451	653	45.0	8.9	22.1	34.7	49.2	<0.01
2	4142	2252	54.4	15.5	33.2	49.1	58.8	
3	3352	1833	54.7	23.3	41.0	50.7	57.6	
Pathologic tumor size								
≤2 cm	4545	2035	44.8	11.1	25.7	38.8	49.8	<0.01
>2 cm	4678	2845	60.8	23.5	42.8	55.6	63.5	
ER status								
ER-negative	2481	1290	52.0	23.3	39.1	47.7	53.1	0.47
ER-positive	5457	2846	52.2	14.0	31.8	47.2	58.5	
ER status and nodal status								
ER-negative and positive nodes	1473	932	63.3	30.6	49.7	58.6	63.0	<0.01
Other (excluding ER unknown)	6465	3204	49.6	13.8	30.5	44.8	55.4	
HER2 Status								
HER2-negative	3263	1278	39.2	11.3	23.8	36.3	46.4	0.07
HER2-positive	608	256	42.1	18.1	31.5	40.0	45.9	
Menopausal status								
Pre menopausal	4763	2435	51.1	17.0	34.7	46.8	54.0	<0.01
Post menopausal	4761	2574	54.1	17.4	33.7	47.7	59.4	

Table 4. (*Continued*)

	No. of patients	No. of events	% of patients	Incidence (%)				
				2-year	5-year	10-year	15-year	*P*
Age								
<35 years	372	228	61.3	26.3	49.5	57.7	60.8	<0.01
35–49 years	3542	1762	49.7	16.3	33.7	46.0	53.1	
50–59 years	2936	1479	50.4	17.1	33.2	45.3	54.7	
≥60 years	2674	1540	57.6	17.2	33.8	49.5	62.8	

Abbreviation: ER, estrogen receptor.

The numbers of patients in the subpopulations not shown were as follows: 579 with tumor grade unknown; 301 with pathologic tumors of unknown size; 1586 ER status unknown; 5653 HER2 unknown.

†Local, regional, distant (except CNS) recurrences, contralateral breast, second primary, death without recurrence, unknown.

at 1 year in our series, although a few patients survive for many years after surgical resection (with or without radiotherapy), in conformity with a randomized study indicating that solitary and hence completely resectable brain metastases should be surgically treated [19]. However, few patients are eligible for surgical resection. Whole brain radiotherapy with local boost have been shown to improve survival compared with whole brain radiotherapy alone for single metastases and to improve local brain control rate for up to 3 or 4 metastases [20]. Our finding of an increased incidence of CNS recurrence among patients with node-positive disease, negative estrogen-receptor status, high-tumor grade and younger age is similar to previous reports [2]. These same factors are well-established prognostic factors for any type of breast cancer recurrence, and not specific to CNS recurrence.

The overall 10-year incidence of CNS recurrence (5.2%) in the present series may seem rather low. However, similar rates (5.1%) have been found in population-based studies [1]. Based on case series, the incidence of clinically evident CNS metastases among women with metastatic breast cancer is estimated to be 10% to 16% [2, 3]. In advanced breast cancer, a high incidence of CNS metastases was found in women treated with taxanes, 14% and 30%, respectively [21, 22]. Similarly, a high incidence (34%) of CNS metastases was found among patients treated with trastuzumab for stage IV breast cancer [23, 24]. Because trastuzumab does not cross the blood-brain barrier [25], this higher incidence may reflect prolongation of disease control in the systemic compartment but not in the CNS. In addition, HER2-positive tumors are known to behave more aggressively, and it may be their biological behavior that results in an increased rate of CNS metastasis. In a nude mouse model meastasis formation by human breast cancer cells was dependent on metastasis-specific genes [26]. Alternatively, it is possible that taxanes and/or trastuzumab could somehow alter the blood brain barrier thereby leading to an increased rate of CNS metastases. Here we report a large series of 9524 patients entered onto adjuvant trials at a time when neither taxanes nor trastuzumab were available for adjuvant treatment. Our finding of a higher incidence of CNS recurrence in the HER2-positive cohort among those with available HER2 status (3871 patients) supports an inherent increased likelihood of CNS metastasis independent of taxane or trastuzumab therapy.

Some authors have expressed the hope that it may become possible to define populations with a risk of CNS recurrence sufficient to justify brain imaging in asymptomatic patients [2, 23]. Although such justification involves subjective judgment, we were unable to define a high-risk group for which the search for occult CNS metastases seemed to us to be justifiable. Even in patients experiencing lung recurrence, the rate of subsequent CNS recurrence was only 10.6% at 2 years and 16.4% at 10 years after the first recurrence.

In our series, HER2 status was available in only 41% of the patients and gene expression profiles were not available at all. It is possible that these factors might help to define groups at high risk for CNS recurrence. The present study is inherently limited by its retrospective nature. Its strengths include the large number of patients treated in prospective protocols which should reduce selection bias thus preventing falsely elevated incidence rates.

Even if we would be able to define a high risk population suitable for screening for occult brain metastases at a reasonable cost, there is at present no evidence that early detection and treatment of asymptomatic CNS relapse would be of clinical benefit. A recent series of 155 patients with metastatic disease screened for occult CNS involvement found 23 (14.8%) patients with occult CNS disease [27]. Although the prognosis of these patients was reduced compared to those without occult CNS disease, there was no evidence that earlier treatment of CNS disease was beneficial. Nevertheless, patients presenting with CNS metastases (and their relatives) frequently express frustration that the metastases were not detected earlier. If screening for occult brain metastases were easy and cost-free, we would probably agree to do it even for such a tiny prospective gain. Therefore, a cost–benefit analysis should be undertaken. In such an analysis, costs would of course include not only dollars but the patient burden of undergoing investigations (including invasive tests in cases which turn out to be false positives) and the burden of earlier knowledge of a dire prognosis. Limited-stage small cell lung cancer in complete remission remains the only disease where prophylactic cranial irradiation is currently justified [28]. Prophylactic cranial irradiation is not justified for any cohort of breast cancer patients at this time.

Table 5. Cumulative incidence of recurrence in CNS at any time (measured from date of randomization)

	No. of patients	No. of events	% of patients	Incidence (%)				
				2-year	5-year	10-year	15-year	*P*
Recurrence in CNS at any time								
Total	9524	517	5.4	1.0	3.3	5.2	5.8	
Nodal status								
Node-negative	4007	130	3.2	0.5	1.9	3.4	3.7	<0.01
1–3 positive nodes	3335	186	5.5	0.8	3.2	5.0	5.7	
≥4 positive nodes	2163	201	9.3	2.3	5.8	8.5	9.3	
Tumor grade								
1	1451	28	2.0	0.1	0.7	1.5	1.9	<0.01
2	4142	200	4.8	0.6	2.5	4.5	5.3	
3	3352	261	7.8	1.9	5.4	7.8	8.2	
Pathologic tumor size								
≤2 cm	4545	179	3.9	0.4	2.1	3.6	4.4	<0.01
>2 cm	4678	324	6.9	1.5	4.4	6.8	7.2	
ER status								
ER-negative	2481	200	8.1	2.3	5.7	7.8	8.4	<0.01
ER-positive	5457	229	4.2	0.5	2.2	4.0	4.6	
ER status and nodal status								
ER-negative and positive nodes	1473	138	9.4	2.8	6.8	8.7	9.6	<0.01
Other	6465	291	4.5	0.7	2.5	4.4	5.9	
HER2 status								
HER2-negative	3263	107	3.3	0.5	1.9	3.5	3.8	<0.01
HER2-positive	608	39	6.4	1.3	4.2	6.8	6.8	
Menopausal status								
Pre menopausal	4763	317	6.7	1.0	3.8	6.2	7.1	<0.01
Post menopausal	4761	200	4.2	1.0	2.8	4.2	4.6	
Age								
<35 years	372	40	10.8	1.9	7.3	10.5	10.9	<0.01
35–49 years	3542	225	6.4	0.9	3.5	5.9	6.8	
50–59 years	2936	164	5.6	1.3	3.4	5.4	6.0	
≥60 years	2674	88	3.3	0.8	2.3	3.3	3.6	
Competing risk: death before recurrence in CNS								
Total	9524	3536	37.1	4.9	16.6	30.3	40.7	
Nodal status								
Node-negative	4007	754	18.8	1.8	7.5	15.8	24.6	<0.01
1–3 positive nodes	3335	1405	41.9	4.4	15.5	30.1	40.9	
≥4 positive nodes	2163	1377	63.7	11.5	34.9	54.6	63.8	
Tumor grade								
1	1451	461	31.8	2.4	6.8	18.8	33.1	<0.01
2	4142	1585	38.3	3.6	14.8	30.7	43.0	
3	3352	1310	39.1	7.8	23.3	35.3	41.5	
Pathologic tumor size								
≤2 cm	4545	1356	29.8	2.8	11.0	23.1	34.4	<0.01
>2 cm	4678	2110	45.1	7.0	22.3	37.9	47.3	
ER status								
ER-negative	2481	913	36.8	8.6	23.4	32.7	37.9	<0.01
ER-positive	5457	1952	35.8	2.9	13.1	29.2	41.8	
ER status and nodal status								
ER-negative and positive nodes	1473	706	47.9	12.5	32.1	42.7	47.8	<0.01
Other	6465	2159	33.4	3.9	12.8	27.5	38.9	
HER2 status								
HER2-negative	3263	816	25.0	2.9	9.8	21.1	31.8	<0.01
HER2-positive	608	185	30.4	5.8	19.7	29.5	32.3	
Menopausal status								
Pre menopausal	4763	1587	33.3	4.5	15.9	27.9	35.7	<0.01
Post menopausal	4761	1949	40.9	5.3	17.3	32.8	45.9	

Table 5. (*Continued*)

	No. of patients	No. of events	% of patients	Incidence (%)				
				2-year	5-year	10-year	15-year	*P*
Age								
<35 years	372	159	42.7	7.8	24.0	36.5	42.8	<0.01
35–49 years	3542	1119	31.6	4.2	15.3	26.9	34.3	
50–59 years	2936	1023	34.8	5.0	16.2	29.0	38.7	
≥60 years	2674	1235	46.2	5.3	17.6	35.4	51.1	

See the corresponding footnote in Table 4.

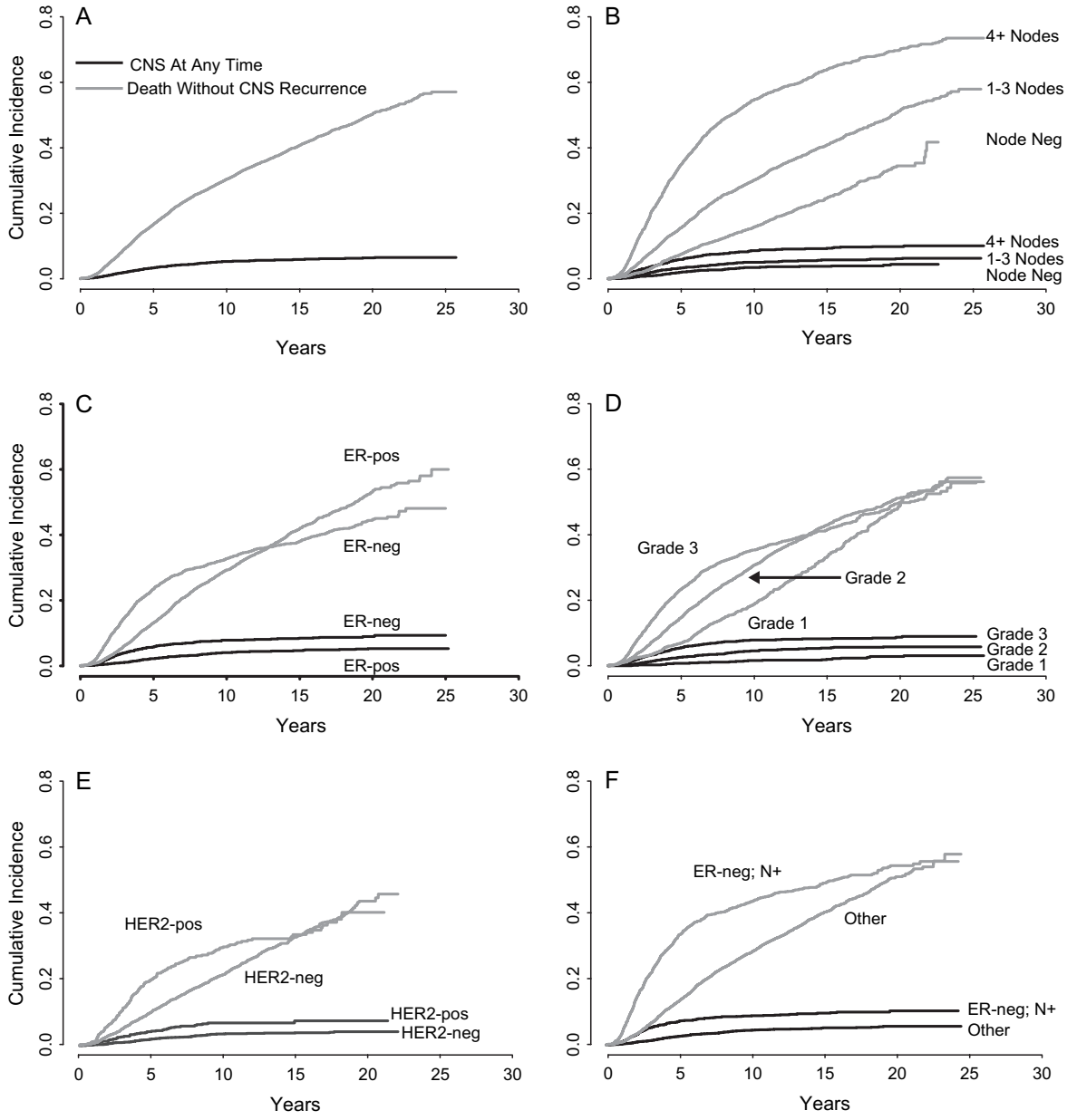

Figure 2. Cumulative incidence of CNS recurrence at any time and death without CNS recurrence, from the time of randomization, among 9524 patients. (**A**) Overall results; (**B**) results according to nodal status (node-negative, $n = 4{,}007$; one to three positive nodes, $n = 3354$; ≥ 4 positive nodes, $n = 2{,}163$); (**C**) results according to ER status (ER-negative, $n = 2481$; ER-positive, $n = 5{,}457$); (**D**) results according to tumor grade (tumor grade 1, $n = 1{,}451$; tumor grade 2, $n = 4{,}142$; tumor grade 3, $n = 3352$); (**E**) results according to HER2 status (HER2-negative, $n = 3{,}263$; HER2-positive, $n = 608$); and (**F**) results according to the high risk cohort of node-positive patients with ER-negative primary tumors ($n = 1473$) versus other (i.e. not node-positive with ER-negative primary tumors) ($n = 6465$).

Table 6. 391 patients who experienced a subsequent CNS metastasis following a first recurrence

Site of first recurrence	No. with site as first recurrence*	No. of CNS mets	% of patients	Cumulative incidence of CNS recurrence after this site (%)		
				2-year	5-year	10-year
Local	796	58	7.3	2.6	6.6	8.2
Contralateral breast	384	11	2.9	0.5	1.6	3.5
Regional	549	74	13.5	6.9	12.7	13.6
Distant: soft tissue, nodes	158	24	15.2	9.0	15.6	15.6
Distant: bone	1,052	85	8.1	4.6	8.0	8.6
Distant: viscera**	1,256	135†	10.7	7.6	10.1	11.4
Second (non-breast) primary	389	4	1.0	0.8	1.2	1.2
Total	4,584	391	8.5	4.9	8.2	9.2

*Unknown sites at first recurrence were excluded ($n = 36$).

**Excluding the 126 CNS events classified as viscera as site of first recurrence.

†Ninety patients (15.6%) experienced a subsequent CNS metastasis following the presence of lung ($n = 577$) metastasis as site of first recurrence. Two-year, 5-year, and 10-year cumulative incidence of CNS recurrence after a lung metastasis was 10.6%, 14.1%, and 16.4%, respectively.

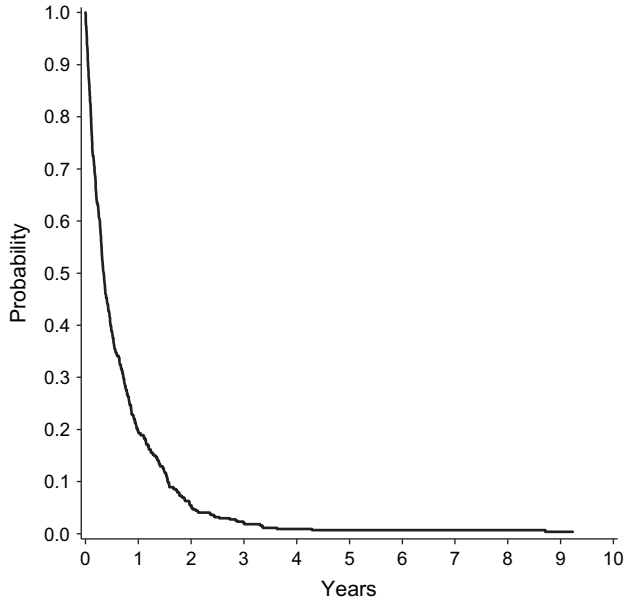

Figure 3. Time from CNS recurrence to death for the 517 patients with CNS recurrence (whether first or subsequent recurrences). One-year survival following CNS recurrence was 20%. Four patients survived more than 4.5 years after CNS recurrence.

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